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Bescheinigung

Certificate

Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten internationalen Patentanmeldung überein.

The attached documents are exact copies of the international patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet international spécifiée à la page suivante.

Den Haag, den
The Hague,
La Haye, le

28. 10. 2003

PRIORITY DOCUMENT
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Der Präsident des Europäischen Patentamts
Im Auftrag
For the President of the European Patent Office
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Patentanmeldung Nr.
Patent application no.
Demande de brevet n°

PCT/EP 02/10417

Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

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Application no.:
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Anmelder:
Applicant(s):
Demandeur(s): 1. Actelion Pharmaceuticals Ltd. - Allschwil - Switzerland

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PCT REQUEST

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IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
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V	**Designation of States**	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	--
V-5	**Precautionary Designation Statement** In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	**Exclusion(s) from precautionary designations**	NONE
VI	**Priority claim**	NONE
VII-1	**International Searching Authority Chosen**	European Patent Office (EPO) (ISA/EP)

Actelion 30/U4

1-PYRIDIN-4-YL-UREA DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to novel 1-pyridin-4-yl urea derivatives of the general formula 1 and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of the general formula 1 and especially their use as neurohormonal antagonists.

BACKGROUND OF THE INVENTION

Urotensin II is a cyclic 11-amino acid peptide that has some sequence similarity to, but is not homologous with, somatostatin-14. Urotensin II was first isolated and sequenced from fish spinal cord (Bern HA, Pearson D, Larson BA, Nishioka RS. Neurohormones from fish tails: the caudal neurosecretory system. I. "Urophysiology" and the caudal neurosecretory system of fishes. Recent Prog. Horm. Res. (1985) 41, 533-552), and has since been found in a wide variety of vertebrate and invertebrate species. Human urotensin II is synthesized in a prepro-form from a single gene located at chromosome 1p36.21, and two cDNA splice variants which differ in their putative signal peptide sequence have been isolated from human colon tumor and human placenta (GenBank Accession Nr. O95399). The putative prohormone convertase dibasic cleavage site is strictly conserved across species. The mature 11-amino acid peptide contains a C-terminal disulfide-bridged 6-amino acid loop which is also strictly conserved, while the N-terminal portion of the mature cyclic peptide can vary considerably across species.

Urotensin II exerts potent and complex hemodynamic actions in mammals (Douglas SA, Sulpizio AC, Piercy V, Sarau HM, Ames RS, Aiyar NV, Ohlstein EH, Willette RN. "Differential vasoconstrictor activity of human urotensin-II in

vascular tissue isolated from the rat, mouse, dog, pig, marmoset and cynomolgus monkey." Br. J. Pharmacol. (2000) 131, 1262-1274. Douglas, SA, Ashton DJ, Sauermelch CF, Coatney RW, Ohlstein DH, Ruffolo MR, Ohlstein EH, Aiyar NV, Willette R "Human Urotensin-II is a potent vasoactive peptide: pharmacological characterization in the rat, mouse, dog and primate." J. Cardiovasc. Pharmacol. (2000) 36, Suppl 1:S163-6). The peptide effectively constricts isolated mammalian arteries. The potency of vasoconstriction is an order of magnitude greater than that of endothelin-1. These effects appear to be mediated at least in part via the actions of urotensin II on a G-protein coupled receptor named GPR14, SENR or UT receptor (Ames RS, et al. "Human urotensin-II is a potent vasoconstrictor and agonist for the orphan receptor GPR14." Nature (1999) 401, 282-6. Mori M, Sugo T, Abe M, Shimomura Y, Kurihara M, Kitada C, Kikuchi K, Shintani Y, Kurokawa T, Onda H, Nishimura O, Fujino M. "Urotensin II is the endogenous ligand of a G-protein-coupled orphan receptor, SENR (GPR14)" Biochem. Biophys. Res. Commun. (1999) 265,123-9. Liu Q, Pong SS, Zeng Z, et al. „Identification of urotensin II as the endogenous ligand for the orphan G-protein-coupled receptor GPR14" Biochem. Biophys. Res. Commun. (1999) 266, 174-178.) The UT receptor is expressed in arterial (but not venous) smooth muscle cells, on atrial and ventricular cardiac myocytes, in pancreas, kidney, and in the brain.

In addition to its vasoconstrictive actions, urotensin II potently affects atrial and ventricular muscle contraction (Russell FD, Molenaar P, and O'Brien DM "Cardiostimulant effects of urotensin-II in human heart in vitro". Br J Pharmacol (2001) 132, 5-9).

Urotensin II stimulates cellular proliferation, migration and collagen synthesis in cardiac fibroblasts (Tzandis A, et al., "Urotensin II stimulates collagen synthesis by cardiac fibroblasts and hypertrophic signaling cardiomyocytes via G(alpha)q- and Ras-dependent pathways". J. Am. Coll. Cardiol. (2001) 37, 164A.) and in neonatal myocytes (Zou Y, Nagai R, and Yamazaki T, "Urotensin II induces hypertrophic responses in cultured cardiomyocytes from neonatal rats". FEBS Lett (2001) 508, 57-60). Urotensin II is produced by cancer cell lines and its receptor is also expressed in these cells. (Takahashi K, et al., "Expression of

urotensin II and urotensin II receptor mRNAs in various human tumor cell lines and secretion of urotensin II-like immunoreactivity by SW-13 adrenocortical carcinoma cells". Peptides (2001) 22, 1175-9).

Urotensin II modulates glucose-stimulated pancreatic release of insulin (Silvestre RA, et al., "Inhibition of insulin release by urotensin II-a study on the perfused rat pancreas". Horm Metab Res (2001) 33, 379-81).

Elevated circulating levels of urotensin II are detected in humans susceptible to high-altitude pulmonary edema, and in patients awaiting kidney transplantation (Totsune K, et al., "Role of urotensin II in patients on dialysis". Lancet (2001) 358, 810-1).

Urotensin II and its receptor are found in spinal cord and brain tissue, and intracerebroventricular infusion of urotensin II into mice induces behavioral changes (Gartlon J, et al., "Central effects of urotensin-II following ICV administration in rats". Psychopharmacology (Berlin) (2001) 155, 426-33).

Substances with the ability to block the actions of urotensin II are accordingly expected to prove useful in the treatment of various diseases. WO-2001/45694 discloses certain sulfonamides as urotensin II receptor antagonists, and their use to treat diseases associated with a urotensin II imbalance. WO-2001/45700 discloses certain pyrrolidines as urotensin II receptor antagonists and their use to treat diseases associated with a urotensin II imbalance. WO-2001/45711 discloses certain pyrrolidine and piperidine derivatives as urotensin II receptor antagonists and their use to treat diseases associated with a urotensin II imbalance. These derivatives are different from the compounds of the present invention as they do not comprise urea derivatives bearing a 4-pyridinyl-like moiety. WO-2002/047687 discloses certain 2-amino-quinolones as urotensin II receptor antagonists and their use to treat diseases associated with a urotensin II imbalance. WO-2002/058702 discloses certain 2-amino-quinolines as urotensin II receptor antagonists and their use to treat diseases associated with a urotensin II imbalance. These derivatives are different from the compounds of the present invention as they do not bear a substituted urea function in the 4-position of the quinoline ring. WO-2001/66143 discloses certain 2,3-dihydro-1H-pyrrolo[2,3-

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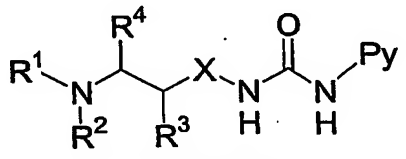
b]quinolin-4-ylamine derivatives useful as urotensin II receptor antagonists, WO-2002/00606 discloses certain biphenyl compounds useful as urotensin II receptor antagonists, and WO-2002/02530 also discloses certain compounds useful as urotensin II receptor antagonists.

The present invention comprises 1-pyridin-4-yl urea derivatives which are novel compositions of matter and which are urotensin II receptor antagonists. EP 428434 discloses certain alkylureidopyridines as neurokinin and substance P antagonists. WO-99/21835 discloses certain ureidoquinolines as H+-ATPase and bone resorption inhibitors. WO-01/009088 discloses certain substituted heteroarylureas as inhibitors of the CCR-3 receptor.

DESCRIPTION OF THE INVENTION

The present invention relates to compounds of the general formula 1,



General Formula 1

wherein:

Py represents quinolin-4-yl which is unsubstituted or mono- or disubstituted independently with lower alkyl or aryl-lower alkyl in the positions 2, 6 or 8; [1,8]naphthyridin-4-yl which is unsubstituted or monosubstituted in position 7 with lower alkyl; pyridin-4-yl which is unsubstituted or disubstituted in positions 2 and 6, whereby the substituent in position 2 is R^5R^6N-, lower alkyl, aryl, aryl-lower alkyl, or aryloxymethyl and the substituent in position 6 is hydrogen or lower alkyl;

X is absent or represents a methylene group;

R^1 represents hydrogen, lower alkyl, aryl-lower alkyl, diaryl-lower alkyl, or aryl;

R^2 forms together with R^3 a five-, six-, or seven-membered ring containing the nitrogen atom to which R^2 is attached as a ring atom and in which case R^4 represents hydrogen; or

defined. Preferred examples of aryl-lower alkyl groups are phenethyl and benzyl and benzyl substituted in the phenyl ring with hydroxy, lower alkyl, lower alkyloxy, or halogen.

The expression 'diaryl-lower alkyl' means a lower alkyl group as previously defined in which two hydrogen atoms have been replaced by an aryl group as previously defined. Preferred examples of diaryl-lower alkyl groups are 2,2-diphenylethyl and 1-benzyl-2-phenyl-ethyl.

The expression 'aryloxymethyl' means a group of the formula aryl-O-CH_2- in which the term 'aryl' has the meaning previously given.

The present invention encompasses pharmaceutically acceptable salts of compounds of the general formula 1. This encompasses either salts with inorganic acids or organic acids like hydrohalogenic acids, e.g. hydrochloric or hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, citric acid, formic acid, acetic acid, maleic acid, tartaric acid, methylsulfonic acid, p- tolylsulfonic acid and the like or in case the compound of formula 1 is acidic in nature with an inorganic base like an alkali or earth alkali base, e.g. sodium, potassium, or calcium salts, etc. The compounds of general formula 1 can also be present in form of zwitterions.

The present invention encompasses different solvation complexes of compounds of general formula 1. The solvation can be effected in the course of the manufacturing process or can take place separately, e.g. as a consequence of hygroscopic properties of an initially anhydrous compound of general formula 1.

The present invention further encompasses different morphological forms, e.g. crystalline forms, of compounds of general formula 1 and their salts and solvation complexes. Particular heteromorphs may exhibit different dissolution properties, stability profiles, and the like, and are all included in the scope of the present invention.

The compounds of the general formula 1 might have one or more asymmetric carbon atoms and may be prepared in form of optically pure enantiomers or

Another group of preferred compounds of general formula 1 consists of those compounds wherein X is absent and R^1, R^2, R^3, R^4, R^5, R^6, and Py have the meaning given in general formula 1 above.

A group of especially preferred compounds of general formula 1 consists of those compounds wherein X is absent, R^3 forms together with R^2 an unsubstituted five-, six-, or seven-membered ring containing the nitrogen atom to which R^2 is attached as a ring atom, R^4 is hydrogen, Py represents quinolin-4-yl, mono- or disubstituted independently with lower alkyl or aryl-lower alkyl in the positions 2 or 8, and R^1 has the meaning given in general formula 1 above.

Another group of especially preferred compounds of general formula 1 consists of those compounds wherein X is absent, R^3 forms together with R^2 an unsubstituted five-, six-, or seven-membered ring containing the nitrogen atom to which R^2 is attached as a ring atom, R^4 is hydrogen, Py represents pyridin-4-yl, substituted in position 2 with R^5R^6N-, wherein R^6 represents aryl-lower alkyl and R^5 represents lower alkyl, and R^1 has the meaning given in general formula 1 above.

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Another group of especially preferred compounds of general formula 1 consists of those compounds wherein X is absent, R^3 forms together with R^2 an unsubstituted five-, six-, or seven-membered ring containing the nitrogen atom to which R^2 is attached as a ring atom, R^4 is hydrogen, R^1 represents diaryl-lower alkyl, and Py has the meaning given in general formula 1 above.

A group of most preferred compounds of general formula 1 consists of those compounds wherein X is absent, R^3 forms together with R^2 an unsubstituted five-, or six-membered ring containing the nitrogen atom to which R^2 is attached as a ring atom, R^4 is hydrogen, and Py, R^1, R^5, and R^6 have the meaning given in general formula 1 above.

Another group of most preferred compounds of general formula 1 consists of those compounds wherein X is absent, R^4 forms together with R^2 an unsubstituted five-, or six-membered ring containing the nitrogen atom to which R^2 is attached as a ring atom, R^3 is hydrogen, and Py, R^1, R^5, and R^6 have the meaning given in general formula 1 above.

Examples of particularly preferred compounds of general formula 1 are:

1-[1-(2,2-Diphenyl-ethyl)-pyrrolidin-3-yl]-3-(2-methyl-quinolin-4-yl)-urea

1-[1-(1-Benzyl-2-phenyl-ethyl)-pyrrolidin-3-yl]-3-(2-methyl-quinolin-4-yl)-urea

like sprays or rectally in form of suppositories. These compounds may also be administered in intramuscular, parenteral or intravenous form, e.g. in form of injectable solutions.

These pharmaceutical compositions may contain the compounds of formula 1 as well as their pharmaceutically acceptable salts in combination with inorganic and/or organic excipients, which are usual in the pharmaceutical industry, like lactose, maize or derivatives thereof, talcum, stearic acid or salts of these materials.

For gelatine capsules vegetable oils, waxes, fats, liquid or half-liquid polyols etc. may be used. For the preparation of solutions and sirups e.g. water, polyols, saccharose, glucose etc. are used. Injectables are prepared by using e.g. water, polyols, alcohols, glycerin, vegetable oils, lecithin, liposomes etc. Suppositories are prepared by using natural or hydrogenated oils, waxes, fatty acids (fats), liquid or half-liquid polyols etc.

The compositions may contain in addition preservatives, stabilisation improving substances, viscosity improving or regulating substances, solubility improving substances, sweeteners, dyes, taste improving compounds, salts to change the osmotic pressure, buffer, anti-oxidants etc.

The compounds of general formula 1 may also be used in combination with one or more other therapeutically useful substances e.g. α- and β-blockers like phentolamine, phenoxybenzamine, atenolol, propranolol, timolol, metoprolol, carteolol, carvedilol, etc.; with vasodilators like hydralazine, minoxidil, diazoxide, flosequinan, etc.; with calcium-antagonists like diltiazem, nicardipine, nimodipine, verapamil, nifedipine, etc.; with angiotensin converting enzyme-inhibitors like cilazapril, captopril, enalapril, lisinopril etc.; with potassium channel activators like pinacidil, chromakalim, etc.; with angiotensin receptor antagonists like losartan, valsartan, candesartan, irbesartan, eprosartan, telmisartan, and tasosartan, etc.; with diuretics like hydrochlorothiazide, chlorothiazide, acetolamide, bumetanide, furosemide, metolazone, chlortalidone, etc.; with sympatholytics like methyldopa, clonidine, guanabenz, reserpine, etc.; with endothelin receptor antagonists like bosentan, tezosentan, darusentan, atrasentan, enrasentan, or sitaxsentan, etc.;

with anti-hyperlipidemic agents like lovastatin, pravistatin, fluvastatin, atorvastatin, cerivastatin, simvastatin, etc.; and other therapeutics which serve to treat high blood pressure, vascular disease or other disorders listed above.

The dosage may vary within wide limits but should be adapted to the specific situation. In general the dosage given daily in oral form should be between about 3 mg and about 3 g, preferably between about 10 mg and about 1 g, especially preferred between 5 mg and 300 mg, per adult with a body weight of about 70 kg. The dosage should be administered preferably in 1 to 3 doses of equal weight per day. As usual children should receive lower doses which are adapted to body weight and age.

GENERAL PREPARATION OF COMPOUNDS OF THE INVENTION

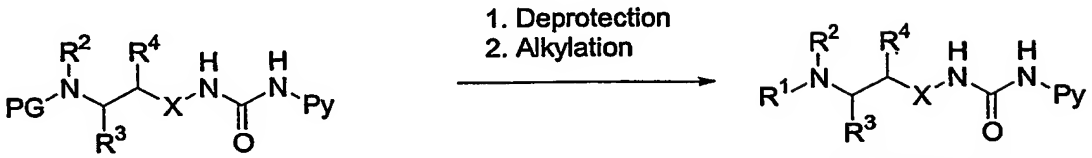
Compounds of the general formula 1 can be prepared using methods generally known in the art, according to the general sequence of reactions outlined below. For simplicity and clarity reasons sometimes only a few of the possible synthetic routes that lead to compounds of general formula 1 are described.

For the synthesis of compounds of general formula 1 general synthetic routes illustrated in Schemes A through D can be employed. The generic groups Py, R^2, R^1, R^3, R^4, R^5, R^6 employed in Schemes A through D have the definitions given in general formula 1 above. In some instances the use of protecting groups (PG) will be required. The use of protecting groups is well known in the art (see for example "Protective Groups in Organic Synthesis, T.W. Greene, P.G.M. Wuts, Wiley-Interscience, 1999). For the purposes of this discussion, it will be assumed that protecting groups such as benzyloxycarbonyl (Cbz), benzyl (Bn) or tert-butyloxycarbonyl (Boc) are in place.

Preparation of compounds of general formula 1.

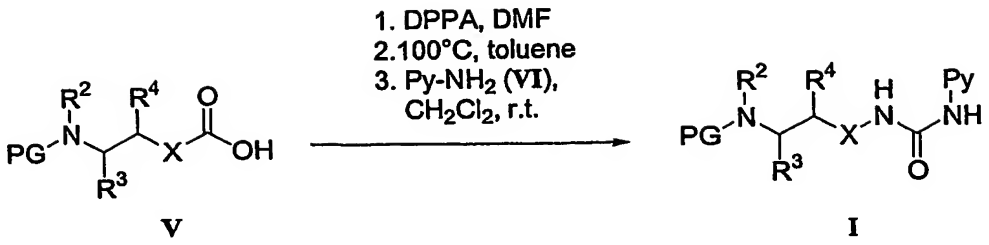
These compounds are prepared according to Scheme A.

Scheme A



1,3-Disubstituted ureas of general structure **I** in Scheme A are deprotected at the nitrogen attached to R^2 according to procedures well known in the art (see for example "Protective Groups in Organic Synthesis, T.W. Greene, P.G.M. Wuts, Wiley-Interscience, 1999) and subsequently alkylated to provide compounds of general formula 1. N-Alkylation is preferentially accomplished by reductive amination, using $NaBHAc_3$ as reducing agent in THF, with aldehydes or ketones that are commercially available or are prepared by methods well-known in the art. Alternatively, N-alkylation can be accomplished, in a polar solvent such as THF in the presence of a small stoichiometric excess of acid scavenger such as Na_2CO_3 or DIPEA, by reaction with halides R^1-X that are commercially available or are prepared by methods well-known in the art. Alternatively, N-alkylation can be accomplished, in a polar solvent such as THF in the presence of a small stoichiometric excess of acid scavenger such as TEA or DIPEA, by reaction with activated carboxylic acid derivatives that are commercially available or are prepared by methods well-known in the art, followed by reduction of the amide intermediate by treatment with a reducing agent such as $LiAlH_4$ in an aprotic solvent such as THF at room temperature.

Scheme D:



V I

Monoprotected, racemic or enantiomerically pure carboxylic acids of general structure **V** are either commercially available or readily prepared by methods well known in the art. 4-Amino-pyridine derivatives of general structure **VI** are commercially available or readily prepared by methods well known in the art. According to Scheme D 4-amino-pyridine derivatives of general structure **VI** are reacted in a solvent such as CH_2Cl_2 with isocyanates, formed in situ from acids of general structure **V** via rearrangement of the derived acyl azides, to provide protected ureas of general structure **I**.

The foregoing general description of the invention will now be further illustrated with a number of non-limiting examples.

EXAMPLES

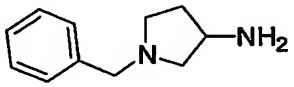
LIST OF ABBREVIATIONS:

AcOH	acetic acid
brine	sat. sodium chloride solution in water
BSA	bovine serum albumin
CDI	carbonyldiimidazole
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DPPA	diphenylphosphorylazide
EDC	*N*-(3-dimethylaminopropyl)-*N'*-ethyl-carbodiimide
EDTA	ethylenediamine tetra-acetic acid
EtOAc	ethyl acetate
Et_2O	diethyl ether
Hex	hexane
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
HV	high vacuum conditions
LC-MS	liquid chromatography-mass spectroscopy
$LiAlH_4$	lithium aluminum hydride

is performed on pre-coated silica gel 60 F_{254} glass-backed plates (Merck). Preparative HPLC is performed on a Varian/Gilson platform using a C18 column of 21 x 60 mm dimensions and a mobile phase consisting of a gradient of 2 - 95% CH_3CN in water containing 0.5% formic acid.

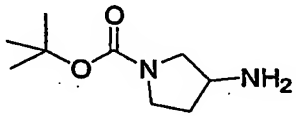
Preparation of Intermediates. Example A.

A1. 1-Benzyl-pyrrolidin-3-ylamine.



This material is commercially available in racemic and both enantiomerically pure forms.

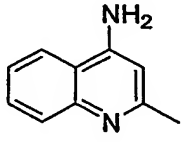
A2. 3-Amino-pyrrolidine-1-carboxylic acid tert-butyl ester.



This material is commercially available in racemic form.

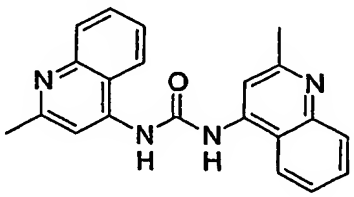
Preparation of Intermediates. Example B.

B1. 4-Amino-2-methylquinoline.



This material is commercially available.

B2. 1,3-Bis-(2-methyl-quinolin-4-yl)-urea.



A solution of 1-(2-methyl-quinolin-4-yl)-3-pyrrolidin-3-yl-urea dihydrochloride (Example C1.2., 51.5 mg, 0.15 mmol), TEA (70 µL, 0.5 mmol), $NaBHAc_3$ (67 mg, 0.32 mmol) and dibenzylketone (42.1 mg, 0.2 mmol) in dry THF (1.5 mL) is stirred at r.t. for 15h, then the solvent is evaporated and the residue purified by prep. HPLC to provide the title compound.

LC-MS (MeCN / H_2O, 1:1) t_R = 0.79 min, m/z = 465.26 (M+1).

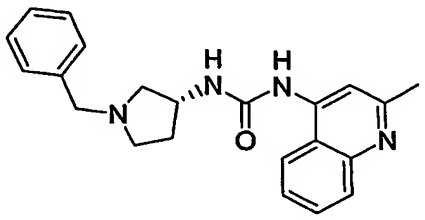
Examples 3-7.

The additional examples set out in the following table are prepared starting from Example C1.2 and commercially available aldehydes using the method of Example 1.

Example No	Example	t_R	$[M+H]^+$
3	1-(2-Methyl-quinolin-4-yl)-3-(1-phenethyl-pyrrolidin-3-yl)-urea	0.71	375.22
4	1-(2-Methyl-quinolin-4-yl)-3-[1-(3-phenyl-propyl)-pyrrolidin-3-yl]-urea	0.73	389.22
5	1-(2-Methyl-quinolin-4-yl)-3-(1-naphthalen-1-ylmethyl-pyrrolidin-3-yl)-urea	0.73	411.19
6	1-(2-Methyl-quinolin-4-yl)-3-(1-naphthalen-2-ylmethyl-pyrrolidin-3-yl)-urea	0.73	411.21
7	1-(1-Biphenyl-4-ylmethyl-pyrrolidin-3-yl)-3-(2-methyl-quinolin-4-yl)-urea	0.76	437.21

Example 8.

(*R*)-1-(1-Benzyl-pyrrolidin-3-yl)-3-(2-methyl-quinolin-4-yl)-urea.



A suspension of (*R*)-1-benzyl-pyrrolidin-3-ylamine (Example A1, 21.0 mg, 0.12 mmol) and 1,3-bis-(2-methyl-quinolin-4-yl)-urea (Example B2, 40.7 mg 0.12 mmol) in MeOH (1 mL) is heated to reflux for 15h. The solvent is evaporated and the residue purified by HPLC to provide the title compound.

LC-MS (MeCN / H_2O, 1:1) t_R = 0.62 min, m/z = 361.16 (M+1).

Example 9.

(*S*)-1-(1-Benzyl-pyrrolidin-3-yl)-3-(2-methyl-quinolin-4-yl)-urea.

The compound is prepared from commercially available (*S*)-1-benzyl-pyrrolidin-3-ylamine (Example A1) and Example B2 as described for Example 8.

LC-MS (MeCN / H_2O, 1:1) t_R = 0.62 min, m/z = 361.14 (M+1).

Example 10.

***rac*-1-(1-Benzyl-pyrrolidin-3-yl)-3-(2-methyl-quinolin-4-yl)-urea.**

The compound is prepared from commercially available *rac*-1-benzyl-pyrrolidin-3-ylamine (Example A1) and Example B2 as described for Example 8.

LC-MS (MeCN / H_2O, 1:1) t_R = 0.69 min, m/z = 361.14 (M+1).

EXAMPLE 11. IN VITRO BIOLOGICAL CHARACTERIZATION

The inhibitory activity of the compounds of general formula 1 on the actions of urotensin II can be demonstrated using the test procedures described hereinafter:

1) INHIBITION OF HUMAN [^{125}I]-UROTENSIN II BINDING TO A RHABDOMYOSARCOMA CELL LINE

Whole cell binding of human [^{125}I]-urotensin II is performed using human-derived TE-671 rhabdomyosarcoma cells (Deutsche Sammlung von Mikroorganismen und Zellkulturen, cell line #ACC-263), by methods adapted from a whole cell endothelin binding assay (Breu V et al., In vitro characterization of Ro-46-2005, a novel synthetic non-peptide antagonist of ET_A and ET_B receptors. FEBS Lett. 1993, 334, 210-214).

The assay is performed in 250 µL Dubecco's modified eagle medium, pH 7.4 (GIBCO BRL, CatNo 31885-023), including 25 mM HEPES (Fluka, CatNo 05473), 1.0 % DMSO (Fluka, CatNo 41644) and 0.5% (w/v) BSA Fraction V (Fluka, CatNo 05473) in polypropylene microtiter plates (Nunc, CatNo 442587). 300'000 suspended cells are incubated with gentle shaking for 4 h at 20°C with 20 pM human [^{125}I]Urotensin II (Anawa Trading SA, Wangen, Switzerland, 2130Ci/mmol) and increasing concentrations of unlabeled antagonist. Minimum and maximum binding are derived from samples with and without 100 nM unlabelled U-II, respectively. After the 4 h incubation period, the cells are filtered onto GF/C filterplates (Packard, CatNo 6005174). The filter plates are dried, and then 50 µL scintillation cocktail (Packard, MicroScint 20, CatNo 6013621) is added to each well. The filterplates are counted in a microplate counter (Packard Bioscience, TopCount NXT).

All test compounds are dissolved and diluted in 100% DMSO. A ten-fold dilution into assay buffer is performed prior to addition to the assay. The final concentration of DMSO in the assay is 1.0%, which is found not to interfere with the binding. IC50 values are defined as the concentration of antagonist inhibiting 50% of the specific binding of [^{125}I]human U-II. Specific binding is the difference

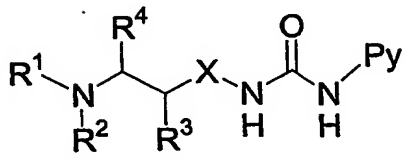
between maximum binding and minimum binding, as described above. An IC_{50} value of 0.206 nM is found for unlabeled human U-II. The compounds of the invention are found to have IC_{50} values ranging from 1 to 1000 nM in this assay.

2) INHIBITION OF HUMAN UROTENSIN II-INDUCED CONTRACTIONS ON ISOLATED RAT THORACIC AORTA :

Adult Wistar rats are anesthetized and exsanguinated. The thoracic aorta is excised, dissected and cut in 3-5 mm rings. The endothelium is removed by gentle rubbing of the intimal surface. Each ring is suspended in a 10 mL isolated organ bath filled with Krebs-Henseleit solution (in mM; NaCl 115, KCl 4.7, $MgSO_4$ 1.2, KH_2PO_4 1.5, $NaHCO_3$ 25, $CaCl_2$ 2.5, glucose 10) kept at 37° C and gassed with 95% O_2 and 5% CO_2. The rings are connected to force transducers and isometric tension is recorded (EMKA Technologies SA, Paris, France). The rings are stretched to a resting tension of 3g. Cumulative doses of human urotensin II (10^{-12} M to 10^{-6} M) are added after a 10 min incubation with the test compound or its vehicle. The functional inhibitory potency of the test compound is assessed by calculating the concentration ratio, i.e. the shift to the right of the EC_{50} induced by a 10^{-5} M concentration of test compound. EC_{50} is the concentration of urotensin needed to get a half-maximal contraction; pA_2 is the negative logarithm of the theoretical antagonist concentration which induces a two-fold shift in the EC_{50} value.

CLAIMS

1. The present invention relates to compounds of the general formula 1,



General Formula 1

wherein:

Py represents quinolin-4-yl which is unsubstituted or mono- or disubstituted independently with lower alkyl or aryl-lower alkyl in the positions 2, 6 or 8; [1,8]naphthyridin-4-yl which is unsubstituted or monosubstituted in position 7 with lower alkyl; pyridin-4-yl which is unsubstituted or disubstituted in positions 2 and 6, whereby the substituent in position 2 is R^5R^6N-, lower alkyl, aryl, aryl-lower alkyl, or aryloxymethyl and the substituent in position 6 is hydrogen or lower alkyl;

X is absent or represents a methylene group;

R^1 represents hydrogen, lower alkyl, aryl-lower alkyl, diaryl-lower alkyl, or aryl;

R^2 forms together with R^3 a five-, six-, or seven-membered ring containing the nitrogen atom to which R^2 is attached as a ring atom and in which case R^4 represents hydrogen; or

R^2 forms together with R^4 a five-, six-, or seven-membered ring containing the nitrogen atom to which R^2 is attached as a ring atom and in which case R^3 represents hydrogen;

the ring formed between R^2 and R^3 or between R^2 and R^4 is unsubstituted or monosubstituted with lower alkyl, aryl, aryl-lower alkyl, hydroxy, or aryloxy;

R^5 and R^6 independently represent hydrogen, lower alkyl, aryl, aryl-lower alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidine, piperidine, or morpholine ring;

and optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, and mixtures of diastereomeric racemates; as well as their pharmaceutically acceptable salts, solvent complexes, and morphological forms.

2. Compounds of general formula 1 in claim 1 wherein R^3 forms together with R^2 an unsubstituted five-, six-, or seven-membered ring containing the nitrogen atom to which R^2 is attached as a ring atom, R^4 is hydrogen and Py, X, and R^1 have the meaning given in general formula 1 above.

3. Compounds of general formula 1 in claim 1 wherein R^4 forms together with R^2 an unsubstituted five-, six-, or seven-membered ring containing the nitrogen atom to which R^2 is attached as a ring atom, R^3 is hydrogen and Py, X, and R^1 have the meaning given in general formula 1 above.

4. Compounds of general formula 1 in claim 1 wherein Py represents quinolin-4-yl, mono- or disubstituted independently with lower alkyl or aryl-lower alkyl in the positions 2 or 8, and R^1, R^2, R^3, R^4, and X have the meaning given in general formula 1 above.

5. Compounds of general formula 1 in claim 1 wherein Py represents pyridin-4-yl, substituted in position 2 with R^5R^6N-, wherein R^6 represents aryl-lower alkyl and R^5 represents lower alkyl, and R^1, R^2, R^3, R^4, R^5, and X have the meaning given in general formula 1 above.

6. Compounds of general formula 1 in claim 1 wherein Py represents pyridin-4-yl, substituted in position 2 with R^5R^6N-, wherein R^6 represents hydrogen and R^1, R^2, R^3, R^4, R^5, and X have the meaning given in general formula 1 above.

7. Compounds of general formula 1 in claim 1 wherein X is absent and R^1, R^2, R^3, R^4, R^5, R^6, and Py have the meaning given in general formula 1 above.

8. Compounds of general formula 1 in claim 1 wherein X is absent, R^3 forms together with R^2 an unsubstituted five-, six-, or seven-membered ring containing the nitrogen atom to which R^2 is attached as a ring atom, R^4 is hydrogen, Py represents quinolin-4-yl, mono- or disubstituted independently with lower alkyl or aryl-lower alkyl in the positions 2 or 8, and R^1 has the meaning given in general formula 1 above.

9. Compounds of general formula 1 in claim 1 wherein X is absent, R^3 forms together with R^2 an unsubstituted five-, six-, or seven-membered ring containing the nitrogen atom to which R^2 is attached as a ring atom, R^4 is hydrogen, Py represents pyridin-4-yl, substituted in position 2 with R^5R^6N-, wherein R^6 represents aryl-lower alkyl and R^5 represents lower alkyl, and R^1 has the meaning given in general formula 1 above.

10. Compounds of general formula 1 in claim 1 wherein X is absent, R^3 forms together with R^2 an unsubstituted five-, six-, or seven-membered ring containing the nitrogen atom to which R^2 is attached as a ring atom, R^4 is hydrogen, Py represents pyridin-4-yl, substituted in position 2 with R^5R^6N-, wherein R^6 represents hydrogen, and R^1, and R^5 have the meaning given in general formula 1 above.

11. Compounds of general formula 1 in claim 1 wherein X is absent, R^4 forms together with R^2 an unsubstituted five-, six-, or seven-membered ring containing the nitrogen atom to which R^2 is attached as a ring atom, R^3 is hydrogen, Py represents quinolin-4-yl, mono- or disubstituted independently with lower alkyl or aryl-lower alkyl in the positions 2 or 8, and R^1 has the meaning given in general formula 1 above.

12. Compounds of general formula 1 in claim 1 wherein X is absent, R^4 forms together with R^2 an unsubstituted five-, six-, or seven-membered ring containing the nitrogen atom to which R^2 is attached as a ring atom, R^3 is hydrogen, Py represents pyridin-4-yl, substituted in position 2 with R^5R^6N-, wherein R^6 represents aryl-lower alkyl and R^5 represents lower alkyl, and R^1 has the meaning given in general formula 1 above.